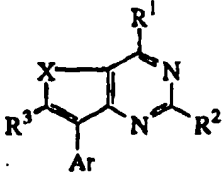




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 495/04, A61K 31/505 // (C07D 495/04, 333:00, 239:00)	A1	(11) International Publication Number: WO 97/29110 (43) International Publication Date: 14 August 1997 (14.08.97)
(21) International Application Number: PCT/EP97/00457 (22) International Filing Date: 30 January 1997 (30.01.97) (30) Priority Data: 60/011,274 7 February 1996 (07.02.96) US 60/027,689 8 October 1996 (08.10.96) US (71) Applicants (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). NEUROCRINE BIOSCIENCES INC. [US/US]; 3050 Science Park Road, San Diego, CA 92121-1102 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CHEN, Chen [CN/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). WEBB, Thomas, R. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). McCARTHY, James, R. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US). MORAN, Terence, J. [US/US]; Neurocrine Biosciences Inc., 3050 Science Park Road, San Diego, CA 92121-1102 (US).		(74) Agent: WANTE, Dirk; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE). (81) Designated States: AL, AM, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: THIOPHENOPYRIMIDINES (57) Abstract <p>This invention concerns compounds of formula (I) including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein X is S, SO or SO₂; R¹ is NR⁴R⁵ or OR⁵; R² is C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkylthio; R³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfoxy or C₁₋₆alkylthio; R⁴ is hydrogen, C₁₋₆alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, C₃₋₆cycloalkyl, C₃₋₆alkenyl, hydroxyC₁₋₆alkyl, C₁₋₆alkylcarbonyloxyC₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl; R⁵ is C₁₋₆alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, Ar¹CH₂, C₁₋₆alkyloxy-C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₃₋₆alkenyl, thienylmethyl, furanyl-methyl, C₁₋₆alkylthioC₁₋₆alkyl, morpholinyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylC₁₋₆alkyl, C₁₋₆alkyl substituted with imidazolyl; or a radical of the formula: -Alk-O-CO-Ar¹; or R⁴ and R⁵ taken together with the nitrogen atom to which they are attached may form an optionally substituted pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group; Ar is a phenyl, substituted phenyl, pyridinyl or substituted pyridinyl; having CRF receptor antagonistic properties; pharmaceutical compositions containing such compounds as active ingredients; methods of treating disorders related to hypersecretion of CRF such as depression, anxiety, substance abuse, by administering an effective amount of a compound of formula (I).</p> <div style="text-align: right; margin-top: 20px;">  <div style="display: inline-block; vertical-align: middle; margin-left: 10px;">(I)</div> </div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CN	Cameroon	LR	Liberia	SN	Senegal
CS	Czechoslovakia	LT	Lithuania	SZ	Swaziland
CZ	Czech Republic	LU	Luxembourg	TD	Chad
DE	Germany	LV	Latvia	TG	Togo
DK	Denmark	MC	Monaco	TJ	Tajikistan
EE	Estonia	MD	Republic of Moldova	TT	Trinidad and Tobago
ES	Spain	MG	Madagascar	UA	Ukraine
FI	Finland	ML	Mali	UG	Uganda
FR	France	MN	Mongolia	US	United States of America
GA	Gabon	MR	Mauritania	UZ	Uzbekistan
				VN	Viet Nam

THIOPHENOPYRIMIDINES

Background of the invention

- 5 This invention relates to thiophenopyrimidines which possess CRF receptor antagonistic properties, to pharmaceutical compositions containing these compounds as active ingredient, and the use thereof in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.
- 10 The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalmi and identified as a 41-amino acid peptide (Vale et al., *Science* 213:1394-1397, 1981). Subsequently, sequences of human and rat CRF were isolated and determined to be identical, but different from ovine CRF in 7 of the 41 amino acid residues (Rivier et al., *Proc. Natl. Acad. Sci. USA* 80:4851, 1983; Shibahara et al., *EMBO J.* 2:775, 1983).
- 15 CRF has been found to produce profound alterations in endocrine, nervous and immune system functions. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotrophic hormone ("ACTH"), β -endorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., *Science* 213:1394-1397, 1981). Briefly, CRF is believed to initiate its biological
- 20 effects by binding to a plasma membrane receptor which has been found to be distributed throughout the brain (DeSouza et al., *Science* 221:1449-1451, 1984), pituitary (DeSouza et al., *Methods Enzymol.* 124:560, 1986; Wynn et al., *Biochem. Biophys. Res. Comm.* 110:602-608, 1983), adrenals (Udelsman et al., *Nature* 319:147-150, 1986) and spleen (Webster, E.L., and E.B. DeSouza, *Endocrinology* 122:609-617, 1988). The CRF receptor is coupled to a GTP-binding protein (Perrin et al., *Endocrinology* 118: 1171- 1179, 1986) which mediates CRF-stimulated increase in intracellular production of cAMP (Bilezikjian, L.M., and W.W. Vale, *Endocrinology* 113:657-662, 1983).
- 30 In addition to its role in stimulating the production of ACTH and POMC, CRF is also believed to coordinate many of the endocrine autonomic, and behavioral responses to stress, and may be involved in the pathophysiology of affective disorders. Moreover, CRF is believed to be a key intermediary in communication between the immune,
- 35 central nervous, endocrine and cardiovascular systems (Crofford et al., *J. Clin. Invest.* 90:2555-2564, 1992; Sapolsky et al., *Science* 238:522-524, 1987; Tilders et al., *Regul. Peptides* 5:77-84, 1982). Overall, CRF appears to be one of the pivotal central nervous system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.

Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment. For example, intracerebroventricular injection of CRF results in
5 behavioral activation (Sutton et al., *Nature* 297:331, 1982), persistent activation of the electroencephalogram (Ehlers et al., *Brain Res.* 2/8332, 1983), stimulation of the sympathoadrenomedullary pathway (Brown et al., *Endocrinology* 110:928, 1982), an increase of heart rate and blood pressure (Fisher et al., *Endocrinology* 110:2222, 1982), an increase in oxygen consumption (Brown et al., *Life Sciences* 30:207, 1982),
10 alteration of gastrointestinal activity (Williams et al., *Am. J. Physiol.* 253:G582, 1987), suppression of food consumption (Levine et al., *Neuropharmacology* 22:337, 1983), modification of sexual behavior (Sirinathsinghji et al., *Nature* 305:232, 1983), and immune function compromise (Irwin et al., *Am. J. Physiol.* 255:R744, 1988). Furthermore, clinical data suggest that CRF may be hypersecreted in the brain in
15 depression, anxiety-related disorders, and anorexia nervosa. (DeSouza, *Ann. Reports in Med. Chem.* 25:215-223, 1990).

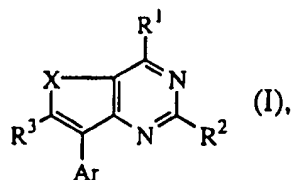
Accordingly, clinical data suggest that CRF receptor antagonists may represent novel antidepressant and/or anxiolytic drugs that may be useful in the treatment of the
20 neuropsychiatric disorders manifesting hypersecretion of CRF. CRF receptor antagonists have been reported in for example, U.S. Patent No. 5,063,245 disclosing substituted 4-thio-5-oxo-3-pyrazoline derivatives and Australian Patent No. AU-A-41399/93, disclosing substituted 2-aminothiazole derivatives. Also, WO-94/13676, WO-94/13677 and WO-95/33750 disclose pyrrolopyrimidines,
25 pyrazolo[3,4-d]pyrimidines and substituted purines as CRF receptor antagonists. EP-0,452,002 discloses thienopyrimidines as pesticides.

Due to the physiological significance of CRF, the development of further biologically active small molecules having significant CRF receptor binding activity and which are
30 capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.

Description of the invention

35 This invention concerns compounds of formula

-3-



including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

- 5 X is S, SO or SO₂;
 R¹ is NR⁴R⁵ or OR⁵;
 R² is C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkylthio;
 R³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfoxy or C₁₋₆alkylthio;
 R⁴ is hydrogen, C₁₋₆alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, C₃₋₆cycloalkyl,
 10 C₃₋₆alkenyl, hydroxyC₁₋₆alkyl, C₁₋₆alkylcarbonyloxyC₁₋₆alkyl or
 C₁₋₆alkyloxyC₁₋₆alkyl;
 R⁵ is C₁₋₆alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, Ar¹CH₂, C₁₋₆alkyloxyC₁₋₆alkyl,
 hydroxyC₁₋₆alkyl, C₃₋₆alkenyl, thienylmethyl, furanylmethyl,
 C₁₋₆alkylthioC₁₋₆alkyl, morpholinyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl,
 15 di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylC₁₋₆alkyl, C₁₋₆alkyl substituted with
 imidazolyl; or a radical of formula -Alk-O-CO-Ar¹;
 or R⁴ and R⁵ taken together with the nitrogen atom to which they are attached may
 form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group,
 optionally substituted with C₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl;
 20 Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected
 from halo, C₁₋₆alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆alkyloxy, benzyloxy,
 C₁₋₆alkylthio, nitro, amino and mono- or di(C₁₋₆alkyl)amino; pyridinyl; pyridinyl
 substituted with 1, 2 or 3 substituents independently selected from halo,
 C₁₋₆alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆alkyloxy, benzyloxy,
 25 C₁₋₆alkylthio, nitro, amino, mono- or di(C₁₋₆alkyl)amino and piperidinyl; and
 wherein said substituted phenyl may optionally be further substituted with one or
 more halogens;
 Ar¹ is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently
 selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, di(C₁₋₆alkyl)aminoC₁₋₆alkyl,
 30 trifluoromethyl and C₁₋₆alkyl substituted with morpholinyl; or pyridinyl; and
 Alk is C₁₋₆alkanediyl.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₁₋₆alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof; C₁₋₂alkyl defines straight saturated hydrocarbon radicals having from 1 to 2 carbon atoms such as methyl and ethyl; C₂₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as ethyl, propyl, butyl, 1-methylethyl and the like; C₃₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 3 to 4 carbon atoms such as propyl, butyl, 1-methylethyl and the like; C₁₋₆alkyl includes C₁₋₂alkyl and C₃₋₄alkyl radicals as defined hereinbefore and the higher homologs thereof having from 5 to 6 carbon atoms such as, pentyl, the pentyl isomers, hexyl and the hexyl isomers; C₁₋₈alkyl includes C₁₋₆alkyl and the higher homologues thereof having from 7 to 8 carbon atoms such as, for example, heptyl, octyl and the like; C₃₋₆alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the like; and where said C₃₋₆alkenyl is linked to a nitrogen or oxygen, the carbon atom making the link preferably is saturated. C₃₋₆cycloalkyl comprises cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. HydroxyC₁₋₆alkyl refers to C₁₋₆alkyl substituted with a hydroxyl group. HomopiperidinyI refers to a 7 membered saturated ring containing one nitrogen atom.

Depending on the nature of some of the substituents, the compounds of formula (I) may contain one or more asymmetric centers which may be designated with the generally used R and S nomenclature.

The compounds of the present invention contain basic nitrogen atoms and, as such, can be present as the free base or in the form of acid addition salts, both being part of this invention. Acid addition salts may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids.

Particular groups of compounds within the invention are those compounds of formula (I) wherein one or more of the following restrictions apply :

- a) R^1 is NR^4R^5 wherein R^4 is C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl, and R^5 is C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} cycloalkylmethyl or hydroxy C_{1-6} alkyl; in particular R^4 is C_{2-4} alkyl or methoxy C_{1-2} alkyl, and R^5 is C_{2-4} alkyl, cyclopropylmethyl or hydroxy C_{2-4} alkyl;
- b) or, R^1 is OR^5 wherein R^5 is C_{1-6} alkyl; in particular C_{2-4} alkyl;
- c) R^2 is C_{1-6} alkyl, in particular C_{1-2} alkyl;
- d) R^3 is hydrogen or C_{1-6} alkyl, in particular hydrogen or C_{1-2} alkyl;
- e) Ar is a phenyl substituted with 1, 2 or 3 substituents each independently selected from C_{1-6} alkyl, C_{1-6} alkyloxy or halo and one of the further hydrogens on said substituted phenyl may be a halo; in particular Ar is phenyl substituted on the 4-, 2,4- or 2,4,6-positions each independently with halo, C_{1-2} alkyl or C_{1-2} alkyloxy; or Ar is a pyridinyl substituted with 1, 2 or 3 substituents each independently selected from di(C_{1-6} alkyl)amino or C_{1-6} alkyl; in particular Ar is pyridinyl substituted on the 2,4-, 2,6- or 2,4,6-positions each independently with di(C_{1-2} alkyl)amino or C_{1-2} alkyl.

Another particular group of compounds are those compounds of formula (I) wherein R^1 is NR^4R^5 and R^4 and R^5 are taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group; optionally substituted with C_{1-6} alkyl or C_{1-6} alkyloxy C_{1-6} alkyl.

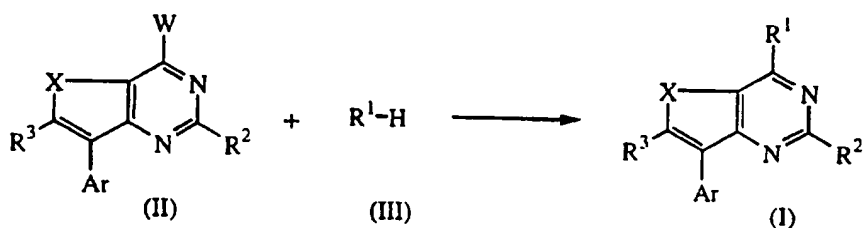
Preferred compounds are those compounds of formula (I) wherein R^1 is NR^4R^5 wherein R^4 is C_{3-4} alkyl or C_{1-2} alkyloxy C_{3-4} alkyl, preferably propyl; and R^5 is C_{3-4} alkyl or cyclopropylmethyl, preferably propyl; or R^1 is OR^5 wherein R^5 is C_{3-4} alkyl; R^2 is methyl; R^3 is hydrogen or methyl; and Ar is substituted in the 2-, 4- and 6-positions with halo or C_{1-4} alkyl and optionally further substituted with a 3-halo; more preferably Ar is 2,4,6-trimethyl-phenyl, 3-bromo-2,4,6-trimethylphenyl, 6-(dimethylamino)-4-methyl-pyridinyl or 2,4-dimethylpyridinyl.

More preferably Ar is 3-pyridinyl substituted in the 4- and/or 6-position with methyl or dimethylamino.

Most preferred are those compounds selected from 2-methyl-6-(*N*-propyl-*N*-cyclopropylamino)-8-(2,4,6-trimethylphenyl)-thiopheno[3,2-*d*]pyrimidine; or

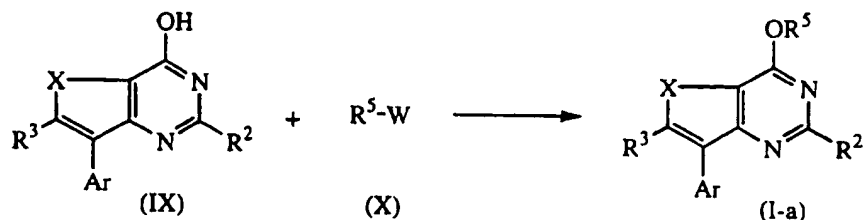
2-methyl-6-(*N,N*-dipropylamino)-8-(2,4,6-trimethylphenyl)-thiopheno[3,2-*d*]pyrimidine; the stereoisomeric forms and the pharmaceutically acceptable acid addition salts thereof.

- 5 The compounds of the present invention can generally be prepared by alkylating a thiazolopyrimidine of formula (II) with an intermediate of formula (III).



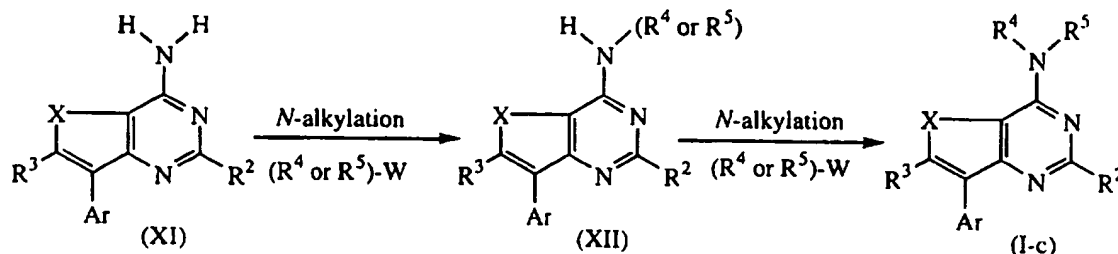
- 10 In intermediate (II), W is an appropriate leaving group such as halo, e.g. chloro, bromo, or a sulfonyloxy group, e.g. a mesyloxy or a tosyloxy group. The above reaction is typically conducted in a suitable solvent, e.g. an aprotic solvent such as DMF or acetonitrile, an ether, e.g. tetrahydrofuran, preferably at an elevated temperature and, when intermediates of formula (III) are volatile amines, in a sealed reaction vial.

- 15 Also, compounds of formula (I) wherein R¹ is OR⁵; said compounds being represented by formula (I-a), may be prepared by *O*-alkylating an intermediate of formula (IX) with an intermediate of formula (X), wherein W is as defined above. Said reaction can be performed in a reaction-inert solvent such as, for example, *N,N*-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, preferably
20 at a temperature ranging between room temperature and reflux temperature.



- 25 The compounds of formula (I) wherein R¹ is NR⁴R⁵, represented by formula (I-c), can be prepared from either compounds of formula (XI) or (XII) by suitable *N*-alkylation reactions as depicted herebelow, wherein W is as previously defined. These *N*-alkylations are conducted in a reaction-inert solvent such as, for example, an ether e.g. tetrahydrofuran and preferably in the presence of a strong base, e.g. NaH.

-7-



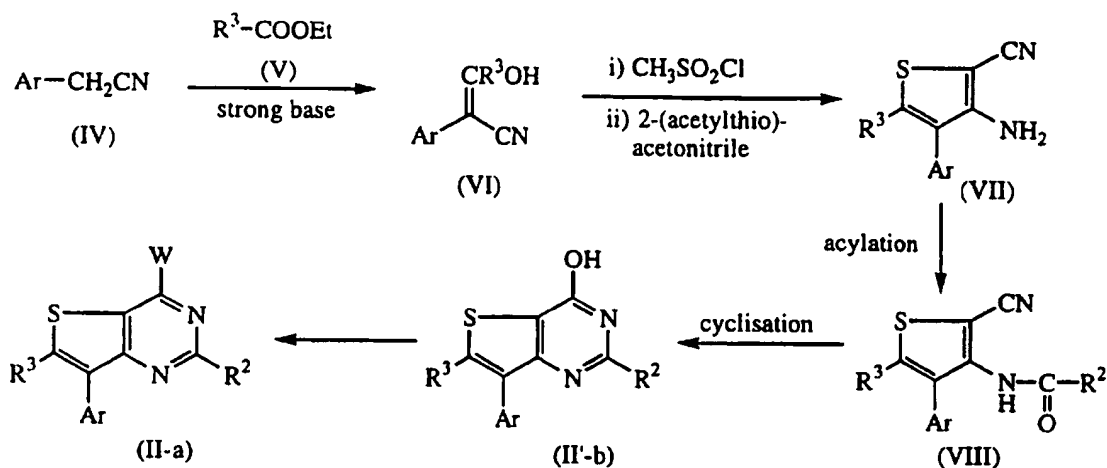
In certain instances, this reaction can give rise to side products wherein R^2 is alkylated by $(\text{R}^4 \text{ or } \text{R}^5)\text{-W}$, in particular where R^2 is methyl and R^4 or R^5 is lower alkyl.

- 5 As outlined below, compounds of formula (I) may be converted into each other following art-known transformation procedures.

- For instance, compounds of formula (I) wherein X is S can be converted into compounds of formula (I) wherein X is SO or SO_2 by an oxidation reaction, e.g.
- 10 treatment with a peroxide such as 3-chloroperbenzoic acid in a reaction-inert solvent, e.g. dichloromethane. By controlling the amount of oxidant and other reaction parameters, either compounds of formula (I) wherein X is SO or X is SO_2 can be obtained, or a mixture of both, which subsequently can be separated by conventional methods, e.g. column chromatography. Also, the compounds of formula (I) wherein R^3
- 15 is C_{1-6} alkylthio can be converted into compounds of formula (I) wherein R^3 is C_{1-6} alkylsulfonyl or C_{1-6} alkylsulfoxy by an oxidation reaction similar as above described. By controlling the amount of oxidant and other reaction parameters, and by separating the end products, the various oxidated products can be separately obtained.
- 20 Further, the Ar group of compounds of formula (I) can be halogenated using a halogenating agent such as, e.g. chlorine or bromine, in a suitable solvent, e.g. acetic acid, and optionally the reaction may be performed at a temperature ranging between room temperature and the reflux temperature of the reaction mixture.
- 25 Stereoisomers may be prepared by separation of the end products of formula (I) following art-known procedures, e.g. by treatment with an optically active acid and separating the thus-formed diastereoisomeric salts by selective crystallization or column chromatography. Or, stereoisomers may be prepared by using stereoisomeric starting materials in any of the above reaction schemes or in the preparation of
- 30 intermediates described hereinafter.

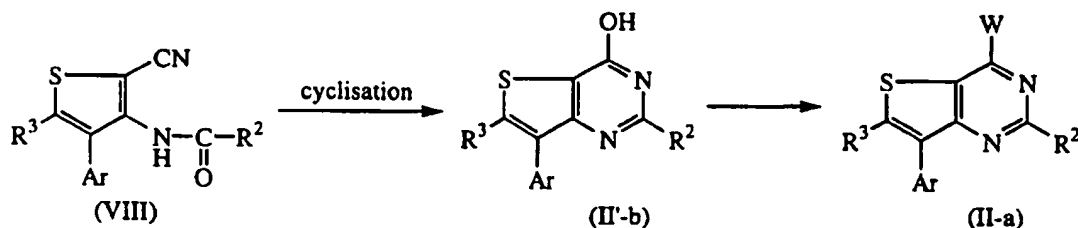
Intermediates of formula (II) wherein X is S, said intermediates being represented by compounds of formula (II-a), can be prepared as outlined herebelow. Intermediates of

formula (VI) are prepared by treating intermediates of formula (IV) with an ester of formula (V) in a reaction-inert solvent such as an alcohol, e.g. ethanol, preferably in the presence of a strong base such as, e.g. sodium ethoxide or sodium hydride. The intermediates (VI) are reacted with methanesulphonyl chloride and subsequently with 2-(acetylthio)-acetonitrile, yielding aminothiophene derivatives of formula (VII). These are converted into intermediates (VIII) using conventional acylation methods such as, e.g. the use of an acid anhydride $(R^2CO)_2O$. Intermediates of formula (VIII) are cyclized to intermediates (II'-b), in which the hydroxy group is converted into leaving group W, e.g. by treating intermediate (II'-b) with methanesulfonyloxy chloride or a halogenating reagent such as, e.g. $POCl_3$, thus yielding intermediates (II-a).



Intermediates of formula (XI) are prepared by treating intermediates of formula (II) with ammonia.

In an embodiment, this invention also provides for compounds of formula (II'-a), defined as compounds of formula (II-a) wherein W' represents hydroxy, halo, mesyloxy or tosyloxy.



Said intermediates of formula (II'-a) may be prepared according to procedures used to prepare intermediates of formula (II-a), thereby thereby yielding compounds of formula

(II'-b), defined as compounds of formula (II'-a) wherein W' is hydroxy; and optionally converting compounds of formula (II'-b) into compounds of formula (II-a), defined as compounds of formula (II'-a) wherein W' is other than hydroxy.

- 5 The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including
- 10 (but not limited to) the assays disclosed by DeSouza et al. (*J. Neuroscience* 7:88, 1987) and Battaglia et al. (*Synapse* 1:572, 1987). As mentioned above, suitable CRF antagonists include compounds which demonstrate CRF receptor affinity. CRF receptor affinity may be determined by binding studies that measure the ability of a compound to inhibit the binding of a radiolabeled CRF (*e.g.* [¹²⁵I]tyrosine CFR) to receptor (*e.g.*,
- 15 receptors prepared from rat cerebral cortex membranes). The radioligand binding assay described by DeSouza et al. (*supra*, 1987) provides an assay for determining a compound's affinity for the CRF receptor. Such activity is typically calculated from the IC₅₀ as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the receptor, and is reported as a "K_i" value calculated by the following
- 20 equation :

$$K_i = \frac{IC_{50}}{1 + L / K_D}$$

where L = radioligand and K_D= affinity of radioligand for receptor (Cheng and Prusoff,

25 *Biochem. Pharmacol.* 22:3099, 1973).

In addition to inhibiting CRF receptor binding, a compound's CRF receptor antagonist activity may be established by the ability of the compound to antagonize an activity associated with CRF. For example, CRF is known to stimulate various biochemical processes, including adenylate cyclase activity. Therefore, compounds may be

30 evaluated as CRF antagonists by their ability to antagonize CRF-stimulated adenylate cyclase activity by, for example, measuring cAMP levels. The CRF-stimulated adenylate cyclase activity assay described by Battaglia et al. (*supra*, 1987) provides an assay for determining a compound's ability to antagonize CRF activity. Accordingly, CRF receptor antagonist activity may be determined by assay techniques which

35 generally include an initial binding assay (such as disclosed by DeSouza (*supra*, 1987)) followed by a cAMP screening protocol (such as disclosed by Battaglia (*supra*, 1987)).

With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a K_i of less than 10 μM . In a preferred embodiment of this invention, a CRF receptor antagonist has a K_i of less than 1 μM , and more preferably less than 0.25 μM (*i.e.*, 250 nM).

5

The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site, and may be used as therapeutic agents for the treatment of a wide range of disorders or illnesses including endocrine, psychiatric, and neurologic disorders or illnesses. More specifically, the CRF receptor antagonists of the present invention may be useful in treating physiological conditions or disorders arising from the hypersecretion of CRF. Because CRF is believed to be a pivotal neurotransmitter that activates and coordinates the endocrine, behavioral and automatic responses to stress, the CRF receptor antagonists of the present invention can be used to treat neuropsychiatric disorders. Neuropsychiatric disorders which may be treatable by the CRF receptor antagonists of this invention include affective disorders such as depression; anxiety-related disorders such as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, cardiovascular abnormalities such as unstable angina and reactive hypertension; and feeding disorders such as anorexia nervosa, bulimia, and irritable bowel syndrome. CRF antagonists may also be useful in treating stress-induced immune suppression associated with various diseases states, as well as stroke. Other uses of the CRF antagonists of this invention include treatment of inflammatory conditions (such as rheumatoid arthritis, uveitis, asthma, inflammatory bowel disease and G.I. motility), Cushing's disease, infantile spasms, epilepsy and other seizures in both infants and adults, and various substance abuse and withdrawal (including alcoholism).

25

In another embodiment of the invention, pharmaceutical compositions containing one or more CRF receptor antagonists are disclosed. For the purposes of administration, the compounds of the present invention may be formulated as pharmaceutical compositions. Pharmaceutical compositions of the present invention comprise a CRF receptor antagonist of the present invention (*i.e.*, a compound of structure (I)) and a pharmaceutically acceptable carrier and/or diluent. The CRF receptor antagonist is present in the composition in an amount which is effective to treat a particular disorder, that is, in an amount sufficient to achieve CRF receptor antagonist activity, and preferably with acceptable toxicity to the patient. Preferably, the pharmaceutical compositions of the present invention may include a CRF receptor antagonist in an

30

35

amount from 0.1 mg to 250 mg per dosage depending upon the route of administration, and more preferably from 1 mg to 60 mg. Appropriate concentrations and dosages can be readily determined by one skilled in the art.

5 Pharmaceutically acceptable carrier and/or diluents are familiar to those skilled in the art. For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to a CRF receptor
10 antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the CRF receptor antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington's Pharmaceutical Sciences*, Gennaro, Ed., Mack Publishing Co., Easton, USA, 1990.

15 In another embodiment, the present invention provides a method for treating a variety of disorders or illnesses, including endocrine, psychiatric and neurologic disorders or illnesses. Such methods include administering of a compound of the present invention to a warm-blooded animal in an amount sufficient to treat the disorder or illness. Such
20 methods include systemic administration of a CRF receptor antagonist of this invention, preferably in the form of a pharmaceutical composition. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions of CRF receptor antagonists include powders, granules, pills, tablets, and capsules as well as liquids, syrups,
25 suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain, in addition to the CRF receptor antagonist, buffers, antioxidants, bacteriostats, and other
30 additives commonly employed in such solutions.

As mentioned above, administration of a compound of the present invention can be used to treat a wide variety of disorders or illnesses. In particular, the compounds of the present invention may be administered to a warm-blooded animal for the treatment of
35 depression, anxiety disorder, panic disorder, obsessive-compulsive disorder, abnormal aggression, unstable angina, reactive hypertension, anorexia nervosa, bulimia, irritable

bowel syndrome, stress-induced immune suppression, stroke, inflammation, Cushing's disease, infantile spasms, epilepsy, and substance abuse or withdrawal.

5 Hence, the use of a compound of formula (I) as a medicine is provided

The following examples are provided for purposes of illustration, not limitation.

Experimental part

10 Hereinafter "THF" means tetrahydrofuran, "DCM" means dichloromethane, "DMSO" means dimethylsulfoxide and "ACN" means acetonitrile.

A. Preparation of the intermediates.

Example A.1

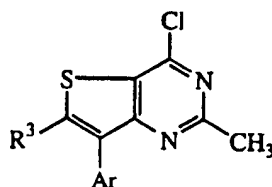
15 a) A solution of 2,4,6-trimethylphenylacetonitrile (75 g) and ethyl formate (67 g) in 225 ml absolute ethanol was treated with solid sodium ethoxide (36 g) in small portions over 10 minutes, with good stirring. The mixture was heated to 60°C under nitrogen for 16 hours and allowed to cool to room temperature. The reaction mixture was poured into 1.2 liters of water, extracted with diethyl ether (3 x 200 ml). The aqueous phase was acidified with 6 M HCl to pH=1 and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried over MgSO₄ and concentrated, yielding 46 g (98%) of 3-hydroxy-2-(2,4,6-trimethylphenyl)acrylonitrile (intermediate 1).

20 b) A solution of intermediate 1 (1 g) in 10 ml pyridine was cooled to 0°C under nitrogen and then treated with methanesulfonyl chloride (0.67 g) with good stirring. The solution was allowed to come to room temperature and stirred for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with 1 M HCl, water and brine, dried (MgSO₄) and concentrated to give 3-methanesulfonyl-2-(2,4,6-trimethylphenyl)acrylonitrile (intermediate 2) as a brown solid (1.4 g).

25 c) To a suspension of NaOEt (3.7 g) in 40 ml of DMSO was added 2-(acetylthio)-acetonitrile. After 30 minutes, a solution of intermediate 2 (13.2 g) in THF (80 ml) was added. LiN(TMS)₂ (1.0 M in THF, 100 ml) was added via a syringe. The reaction was quenched with approximately 1 equivalent of acetic acid, after 1 hour at room temperature. After removing most of the THF by evaporation, the residue was dissolved in 500 ml of ethyl acetate and extracted twice with 500 ml water. The crude 2-cyano-3-amino-4-(2,4,6-trimethylphenyl)-thiophene (intermediate 3) (6.0 g) was carried on to
35 the next step without further purification.

- d) To a solution of intermediate 3 (6.0 g) in acetic acid (6 ml) was added acetic anhydride (5 g). The reaction mixture was stirred for 1 hour at 110°C. After cooling, the crude mixture was poured into a mixture of ethyl acetate (400 ml), water (600 ml) and saturated NaHCO₃ (200 ml). The organic layer was rinsed with water and concentrated. The residue was purified by column chromatography on SiO₂ (gradient; hexane: diethyl ether=2:1 to hexane:ethyl acetate=1:1) to give *N*-[2-cyano-4-(2,4,6-trimethylphenyl)-thiophen-3-yl]-acetamide (intermediate 4).
- e) A suspension of intermediate 4 (2.8 g) in 85% of H₃PO₄ (2 ml) was stirred under nitrogen with an oil bath temperature of 130°C for 30 minutes. After cooling, 20 ml of water was poured into this mixture. After mixing to induce precipitation, the resulting solid was filtered and dried in a vacuum oven to give 2.7 g of 3-methyl-6-hydroxy-8-(2,4,6-trimethylphenyl)-thiopheno[3,2-*d*]pyrimidine (intermediate 5).
- f) A suspension of intermediate 5 (2.6 g) in POCl₃ (8.0 g) was stirred for 2 hours at 100°C. After cooling, the mixture was poured into a mixture of saturated NaHCO₃ and DCM (100 ml). The organic phase was removed, concentrated *in vacuo* and the residue was purified by column chromatography on SiO₂ (gradient; ethyl acetate:hexane=1:4 to ethyl acetate:methanol = 4:1) to give 0.3 g of 2-methyl-6-chloro-8-(2,4,6-trimethylphenyl)-thiopheno[3,2-*d*]pyrimidine (intermediate 6).
- Table 1 lists the intermediates that were prepared according to example A.1.

Table 1 :



Interm. No.	R ³	Ar
6	CH ₃	2,4,6-trimethylphenyl
7	CH ₃	2,6-dimethyl-3-pyridinyl
8	CH ₃	4-chlorophenyl
9	CH ₃	6-(dimethylamino)-4-methyl-3-pyridinyl
10	CH ₃	6-(diethylamino)-4-methyl-3-pyridinyl
11	CH ₃	4,6-dimethyl-3-pyridinyl
12	H	2,4,6-trimethyl-3-pyridinyl
13	H	6-(dimethylamino)-2,4-dimethyl-3-pyridinyl

Interm. No.	R ³	Ar
14	H	2,4,6-trimethylphenyl
15	CH ₃	4-methoxyphenyl
16	CH ₃	2,4-dimethoxyphenyl

B. Preparation of the final products.

Example B.1

A solution of intermediate 6 (20 mg) with *N,N*-dipropylamine in a 3 ml reaction vial was stirred at 120°C. After 1 hour the reaction mixture was cooled, 0.5 ml of acetonitrile was added and refluxed for another 30 minutes. The resulting suspension was allowed to cool to room temperature and diluted with additional acetonitrile. The residue was purified using SiO₂ column chromatography (diethyl ether/hexanes) to give 2-methyl-6-(*N,N*-dipropylamino)-8-(2,4,6-trimethylphenyl)-thiopheno[3,2-*d*]pyrimidine (compound 1).

Example B.2

Treatment of intermediate 6 with sodium hydride and 2-propanol in THF and purification using SiO₂ column chromatography gave 2-methyl-6-(isopropoxy)-8-(2,4,6-trimethyl-phenyl)-thiopheno[3,2-*d*]pyrimidine (compound 6).

Example B.3

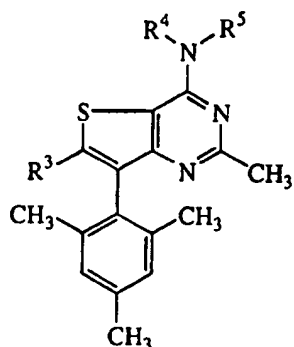
A solution of compound 1 (5 mg) in 1 ml DCM was treated with *meta*-chloro-perbenzoic acid (20 mg). This solution was stirred for 24 hours, then poured into a mixture of ethyl acetate and water. The organic phase was washed with 5% aqueous NaHCO₃ solution and brine, dried (MgSO₄) and concentrated. The residue was purified by preparative TLC (diethyl ether/hexane : 1/9) to give 2-methyl-6-(*N,N*-dipropylamino)-8-(2,4,6-trimethylphenyl)-thiopheno[3,2-*d*]pyrimidine-*S,S*-dioxide (compound 7).

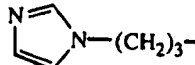
Example B.4

Compound 2 (0.05 mmol) was stirred with excess bromine in 1 ml of acetic acid at room temperature for 30 minutes. The mixture was poured into a mixture of DCM and saturated aqueous NaHCO₃ and the organic layer was evaporated. The residue was purified by SiO₂ chromatography (diethyl ether/hexane), yielding 2-methyl-6-(*N*-propyl-*N*-cyclopropylamino)-8-(3-bromo-2,4,6-trimethylphenyl)-thiopheno[3,2-*d*]pyrimidine (compound 5).

Tables 2, 3 and 4 list the compounds that were prepared according to one of the above Examples and table 5 and 6 list the analytical data for these compounds.

5 Table 2 :



Co. No.	Ex. No.	R ³	R ⁴	R ⁵
1	B.1	H	n-propyl	n-propyl
2	B.1	H	n-propyl	cyclopropylmethyl
3	B.1	H	hydrogen	3-pentyl
4	B.1	H	n-propyl	2-methoxyethyl
9	B.1	H	hydrogen	(CH ₃) ₂ N(CH ₂) ₃
10	B.1	H	CH ₃ O(CH ₂) ₂	CH ₃ O(CH ₂) ₂
11	B.1	H	hydrogen	4-methoxyphenylmethyl
12	B.1	H	hydrogen	CH ₃ O(CH ₂) ₂
13	B.1	H	n-propyl	2-hydroxyethyl
14	B.1	H	hydrogen	4-trifluoromethylphenylmethyl
15	B.1	H	hydrogen	3-hydroxypropyl
16	B.1	H	hydrogen	1-hydroxy-2-hexyl
17	B.1	H	hydrogen	1-hydroxy-2-pentyl
18	B.1	H	hydrogen	
19	B.1	H	hydrogen	CH ₃ CH ₂ -S-(CH ₂) ₂
20	B.1	H	hydrogen	CH ₃ -S-(CH ₂) ₂
21	B.1	H	hydrogen	(CH ₃) ₂ N
22	B.1	H	hydrogen	2-ethoxyphenylmethyl
23	B.1	H	n-propyl	CH ₃ CH ₂ -CO-(CH ₂) ₂
24	B.1	H	hydrogen	n-propyl
25	B.1	H	hydrogen	butyl
26	B.1	H	ethyl	3-hydroxypentyl

-16-

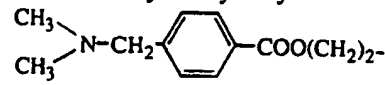
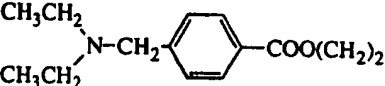
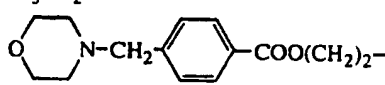
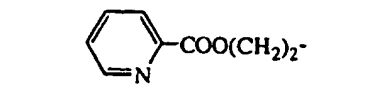
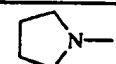
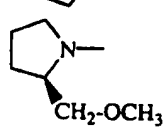
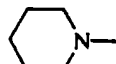
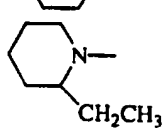
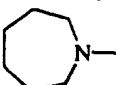
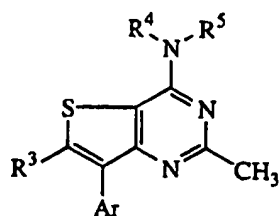
Co. No.	Ex. No.	R ³	R ⁴	R ⁵
27	B.1	H	n-propyl	3-hydroxypentyl
28	B.1	H	n-butyl	3-hydroxypentyl
29	B.1	H	n-propyl	3-hydroxybutyl
30	B.1	H	n-butyl	3-hydroxybutyl
31	B.1	H	n-propyl	
32	B.1	H	n-propyl	
33	B.1	H	n-propyl	
34	B.1	H	n-propyl	
35	B.1	H	hydrogen	4-morpholinyl
Co. No.	Ex. No.	R ³	R ⁴ and R ⁵ taken together	
36	B.1	H		
37	B.1	H		
38	B.1	H		
39	B.1	H		
40	B.1	H		

Table 3 :



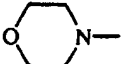
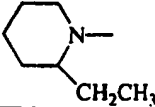
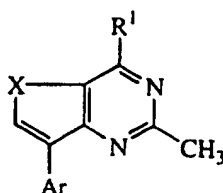
Co. No.	Ex. No.	R ³	R ⁴	R ⁵	Ar
5	B.4	H	n-propyl	cyclopropylmethyl	3-bromo-2,4,6-trimethylphenyl
8	B.1	CH ₃	n-propyl	n-propyl	2,6-dimethyl-3-pyridinyl
41	B.1	CH ₃	n-propyl	n-propyl	4-chlorophenyl
42	B.1	CH ₃	n-propyl	2-hydroxyethyl	4-chlorophenyl
43	B.1	CH ₃	n-propyl	n-propyl	6-(dimethylamino)-4-methyl-3-pyridinyl
44	B.1	CH ₃	n-propyl	n-propyl	6-(diethylamino)-4-methyl-3-pyridinyl
45	B.1	CH ₃	n-propyl	n-propyl	4-methoxyphenyl
46	B.1	CH ₃	n-propyl	2-methoxyethyl	4-methoxyphenyl
47	B.1	CH ₃	2-methoxyethyl	2-methoxyethyl	4-methoxyphenyl
48	B.1	CH ₃	n-propyl	n-propyl	2,4-dimethoxyphenyl
49	B.1	CH ₃	2-methoxyethyl	2-methoxyethyl	2,4-dimethoxyphenyl
50	B.1	CH ₃	n-propyl	n-propyl	4,6-dimethyl-3-pyridinyl
51	B.1	CH ₃	ethyl	n-butyl	4,6-dimethyl-3-pyridinyl
52	B.1	CH ₃	n-propyl	cyclopropylmethyl	4,6-dimethyl-3-pyridinyl
53	B.1	H	n-propyl	cyclopropylmethyl	6-(dimethylamino)-2,4-dimethyl-3-pyridinyl
54	B.1	H	n-propyl	n-propyl	6-(dimethylamino)-2,4-dimethyl-3-pyridinyl
55	B.1	H	n-propyl	2-hydroxyethyl	2,4,6-trimethylphenyl
56	B.1	H	n-propyl	CH ₃ COO(CH ₂) ₂	2,4,6-trimethylphenyl
57	B.1	H	n-propyl	2-hydroxypropyl	2,4,6-trimethylphenyl
58	B.1	H	n-propyl	n-propyl	2,4,6-trimethylphenyl
Co. No.	Ex. No.	R ³	R ⁴ and R ⁵ taken together		Ar
59	B.1	H			2,4,6-trimethylphenyl
60	B.1	CH ₃			4-chlorophenyl

Table 4 :



Co. No.	Ex. No.	X	R ¹	Ar
6	B.2	S	(CH ₃) ₂ CH-O-	2,4,6-trimethylphenyl
7	B.3	SO ₂	(CH ₃ CH ₂ CH ₂) ₂ N-	2,4,6-trimethylphenyl

5

Table 5 : Analytical data

Co. No.	¹ H NMR data (CDCl ₃)
1	δ 0.98 (t, J=7.0 Hz, 6H), 1.76 (m, 4H), 1.99 (s, 6H), 2.30 (s, 3H), 2.45 (s, 3H), 3.69 (t, J= 7.5Hz, 6H), 6.93 (s, 2H), 7.36 (s, 1H)
2	δ 0.37 (m, 2H), 0.59 (m, 2H), 1.02 (t, J=7.5Hz, 3H), 1.25 (m, 1H), 1.85 (m, 2H), 2.01 (s, 6H), 2.34 (s, 3H), 2.48 (s, 3H), 3.69 (d, 2H), 3.80 (m, 2H), 6.96 (s, 2H), 7.40 (s, 1H)
3	δ 0.97 (t, J=7.0 Hz, 6H), 1.70 (m, 4H), 2.01 (s, 6H), 2.31 (s, 3H), 2.50 (s, 3H), 4.40 (m, 1H), 6.94 (s, 2H), 7.36 (s, 1H)
4	δ 1.03 (t, J=7.0 Hz, 6H), 1.79 (m, 2H), 2.01 (s, 6H), 2.34 (s, 3H), 2.47 (s, 3H), 3.41 (s, 3H), 3.73 (t, J=7.5 Hz, 2H), 3.80 (t, J=7.0 H, 2H), 3.97 (t, J=7.0 Hz, 2H), 6.97 (s, 2H), 7.41 (s, 1H)
5	δ 0.37 (m, 2H), 0.59 (m, 2H), 1.02 (t, J=7.5 Hz, 3H), 1.25 (m, 1H), 1.85 (m, 2H), 1.95 (s, 3H), 2.10 (s, 3H), 2.43 (s, 3H), 2.48 (s, 3H), 3.69 (d, 2H), 3.80 (m, 2H), 7.04 (s, 1H), 7.37 (s, 1H)
6	δ 1.45 (d, J=6.5 Hz, 6H), 1.99 (s, 6H), 2.32 (s, 3H), 2.60 (s, 3H), 5.75 (m, 1H), 6.95 (s, 2H), 7.40 (s, 1H)
8	δ 0.98 (t, J=7.0 Hz, 6H), 1.76 (m, 4H), 1.99 (s, 6H), 2.30 (s, 3H), 2.45 (s, 3H), 3.69 (t, J = 7.5 Hz, 6H), 7.08 (d, H), 7.38 (d, 1H)
48	δ 0.97 (t, 6H), 1.76 (m, 4H), 2.37 (s, 3H), 2.47 (s, 3H), 3.68 (t, 4H), 3.74 (s, 3H), 3.86 (s, 3H), 6.61 (2H), 7.22 (2H)
49	δ 2.37 (s, 3H), 2.47 (s, 3H), 3.38 (s, 6H), 3.70 (t, 4H), 3.74 (s, 3H), 3.86 (s, 3H), 4.03 (t, 4H), 6.61 (2H), 7.22 (2H)
56	δ 1.05 (t, 3H), 1.89 (m, 2H), 2.00 (s, 6H), 2.07 (s, 3H), 2.35 (s, 3H), 2.48 (s, 3H), 3.81 (t, 2H), 3.99 (t, 2H), 4.48 (t, 2H), 6.97 (2H), 7.47 (1H)

Table 6 : Analytical data

Co. No.	Mass spectral data	Co. No.	Mass spectral data
9	368 (M ⁺)	35	368 (MH ⁺)
10	399 (M ⁺)	36	337 (M ⁺)
11	403 (M ⁺)	37	382 (MH ⁺)
12	341 (M ⁺)	38	351 (M ⁺)
13	370 (MH ⁺)	39	379 (M ⁺)
14	441 (M ⁺)	40	365 (M ⁺)
15	342 (MH ⁺)	41	373 (M ⁺)
16	384 (MH ⁺)	42	376 (MH ⁺)
17	370 (MH ⁺)	43	397 (M ⁺)
18	392 (MH ⁺)	44	425 (M ⁺)
19	371 (M ⁺)	45	369 (M ⁺)
20	357 (M ⁺)	46	385 (M ⁺)
21	327 (MH ⁺)	47	410 (M ⁺)
22	417 (M ⁺)	48	-
23	410 (MH ⁺)	49	-
24	326 (MH ⁺)	50	368 (M ⁺)
25	340 (MH ⁺)	51	368 (M ⁺)
26	398 (MH ⁺)	52	380 (M ⁺)
27	412 (MH ⁺)	53	409 (M ⁺)
28	426 (MH ⁺)	54	397 (M ⁺)
29	398 (MH ⁺)	55	372 (M ⁺)
30	412 (MH ⁺)	56	-
31	531 (MH ⁺)	57	372 (M ⁺)
32	559 (MH ⁺)	58	368 (M ⁺)
33	573 (MH ⁺)	59	353 (M ⁺)
34	475 (MH ⁺)	60	385 (M ⁺)

C. Pharmacological examples

5 Example C.1 : REPRESENTATIVE COMPOUNDS HAVING CRF RECEPTOR BINDING ACTIVITY

Compounds were evaluated for binding activity to the CRF receptor by a standard radioligand binding assay as generally described by DeSouza et al. (*J. Neurosci.* 7:88-100, 1987). By utilizing various radiolabeled CRF ligands, the assay may be used

to evaluate the binding activity of the compounds of the present invention with any CRF receptor subtype. Briefly, the binding assay involves the displacement of a radiolabeled CRF ligand from the CRF receptor. More specifically, the binding assay was performed in 1.5 ml Eppendorf tubes using approximately 1×10^6 cells per tube stably transfected with human CRF receptors. Each tube received about 0.1 ml of assay buffer (*e.g.*, Dulbecco's phosphate buffered saline, 10 mM magnesium chloride, 20 μ M bacitracin) with or without unlabeled sauvagine, urotensin I or CRF (final concentration, 1 μ M) to determine nonspecific binding, 0.1 ml of [125 I] tyrosine - ovine CRF (final concentration ~200 pM or approximately the K_D as determined by Scatchard analysis) and 0.1 ml of a membrane suspension of cells containing the CRF receptor. The mixture was incubated for 2 hours at 22°C followed by the separation of the bound and free radioligand by centrifugation. Following two washes of the pellets, the tubes were cut just above the pellet and monitored in a gamma counter for radioactivity at approximately 80% efficiency. All radioligand binding data were analyzed using a non-linear least-square curve-fitting program. Binding activity corresponds to the concentration (nM) of the compound necessary to displace 50% of the radiolabeled ligand from the receptor. All compounds as listed in Tables 2 - 4 have a $K_i \leq 250$ nM. Compounds 1, 2, 8, 10, 12 - 18, 20, 23, 34, 35, 37 - 41, 43, 48 - 56 were found to show the best score in this test.

Example C.2

CRF STIMULATED ADENYLATE CYCLASE ACTIVITY

The compounds of the present invention may also be evaluated by various functional testing. For example, the compounds of the present invention may be screened for CRF-stimulated adenylate cyclase activity. An assay for the determination of CRF-stimulated adenylate cyclase activity may be performed as generally described by Battaglia et al. (*Synapse* 1:572, 1987), with modifications to adapt the assay to whole cell preparations.

More specifically, the standard assay mixture may contain the following in a final volume of 0.5 ml: 2 mM L-glutamine, 20 mM HEPES, and 1 mM IMBX in DMEM buffer. In stimulation studies, whole cells with the transfected CRF receptors are plated in 24-well plates and incubated for 1 hour at 37°C with various concentrations of CRF-related and unrelated peptides in order to establish the pharmacological rank-order profile of the particular receptor subtype. Following the incubation, the medium is aspirated, the wells rinsed once gently with fresh medium, and the medium aspirated. To determine the amount of intracellular cAMP, 300 μ l of a solution of 95% ethanol

and 20 mM aqueous hydrochloric acid is added to each well and the resulting suspensions are incubated at -20°C for 16 to 18 hours. The solution is removed into 1.5 ml Eppendorf tubes and the wells washed with an additional 200 µl of ethanol/aqueous hydrochloric acid and pooled with the first fraction. The samples are lyophilized and
5 then resuspended with 500 µl sodium acetate buffer. The measurement of cAMP in the samples is performed using a single antibody kit. For the functional assessment of the compounds, a single concentration of CRF or related peptides causing 80% stimulation of cAMP production is incubated along with various concentrations of competing compounds (10^{-12} to 10^{-6} M).

10

D. Composition examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

15 "Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable acid or base addition salt or a stereochemically isomeric form thereof.

Example D.1 : Oral solutions

20 9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are
25 dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution is filled in suitable containers.

Example D.2 : Capsules

30 20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I..

35

Example D.3 : Film-coated tabletsPreparation of tablet core

- A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose and 15 g hydrogenated vegetable oil. The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

- To a solution of 10 g methyl cellulose in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

Example D.4 : Injectable solution

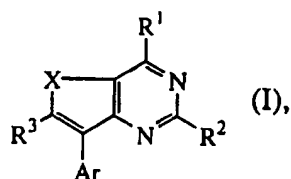
- 1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg/ml of A.I. The solution was sterilized by filtration and filled in sterile containers.

Example D.5 : Suppositories

- 3 Grams A.I. was dissolved in a solution of 3 grams 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 Grams surfactant and 300 grams triglycerides were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37 to 38°C to form 100 suppositories each containing 30 mg/ml of the A.I.

Claims

1. A compound of formula



5

including the stereoisomers and the pharmaceutically acceptable acid addition salt forms thereof, wherein

X is S, SO or SO₂;

R¹ is NR⁴R⁵ or OR⁵;

10 R² is C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkylthio;

R³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylsulfonyl, C₁₋₆alkylsulfoxy or C₁₋₆alkylthio;

R⁴ is hydrogen, C₁₋₆alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, C₃₋₆cycloalkyl, C₃₋₆alkenyl, hydroxyC₁₋₆alkyl, C₁₋₆alkylcarbonyloxyC₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl;

15 R⁵ is C₁₋₈alkyl, mono- or di(C₃₋₆cycloalkyl)methyl, Ar¹CH₂, C₃₋₆alkenyl, C₁₋₆alkyloxyC₁₋₆alkyl, hydroxyC₁₋₆alkyl, thienylmethyl, furanylmethyl, C₁₋₆alkylthioC₁₋₆alkyl, morpholinyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylC₁₋₆alkyl, C₁₋₆alkyl substituted with imidazolyl; or a radical of formula -Alk-O-CO-Ar¹;

20 or R⁴ and R⁵ taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl;

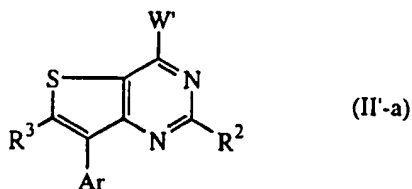
Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C₁₋₆alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆alkyloxy,

25 benzyloxy, C₁₋₆alkylthio, nitro, amino and mono- or di(C₁₋₆alkyl)amino; pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents independently selected from halo, C₁₋₆alkyl, trifluoromethyl, hydroxy, cyano, C₁₋₆alkyloxy, benzyloxy, C₁₋₆alkylthio, nitro, amino, mono- or di(C₁₋₆alkyl)amino and piperidinyl; and wherein said substituted phenyl may optionally be further substituted with one or more halogens;

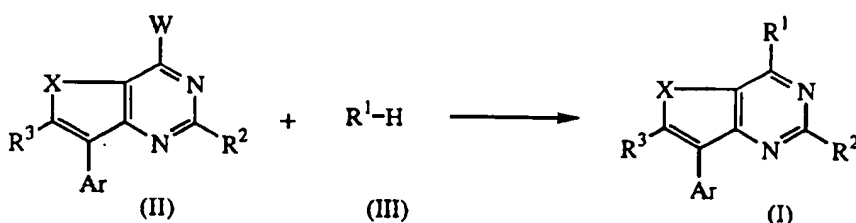
30 Ar¹ is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, trifluoromethyl, and C₁₋₆alkyl substituted with morpholinyl; or pyridinyl; and Alk is C₁₋₆alkanediyl.

2. A compound according to claim 1 wherein R¹ is OR⁵ and R⁵ is C₁₋₆alkyl; or R¹ is NR⁴R⁵ and R⁴ is hydrogen, C₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl, and R⁵ is C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₃₋₆alkenyl or C₃₋₆cycloalkylmethyl; or R¹ is NR⁴R⁵ and R⁴ and R⁵ are taken together with the nitrogen atom to which they are attached to form a pyrrolidiny, piperidiny, homopiperidiny or morpholiny group; optionally substituted with C₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkyl; R² is C₁₋₆alkyl; R³ is hydrogen or C₁₋₆alkyl; and Ar is a phenyl substituted with 1, 2 or 3 substituents each independently selected from C₁₋₆alkyl, C₁₋₆alkyloxy or halo, or Ar is a pyridiny substituted with 1, 2 or 3 substituents each independently selected from C₁₋₆alkyl or di(C₁₋₆alkyl)amino.
3. A compound according to any of claims 1 to 2 wherein R¹ is NR⁴R⁵ wherein R⁴ is C₂₋₄alkyl or methoxyC₁₋₂alkyl; R⁵ is C₂₋₄alkyl, cyclopropylmethyl or hydroxy-C₂₋₄alkyl; R² is C₁₋₂alkyl; R³ is hydrogen or C₁₋₂alkyl.
4. A compound according to any of claims 1 to 2 wherein R¹ is NR⁴R⁵ wherein R⁴ is C₂₋₄alkyl; R⁵ is C₃₋₄alkyl or cyclopropylmethyl; R² is methyl; R³ is hydrogen or methyl; and Ar is 3-pyridiny substituted on the 4- and/or 6-position with methyl or dimethylamino.
5. A compound according to claim 1 wherein the compound is 2-methyl-6-(*N*-propyl-*N*-cyclopropylamino)-8-(2,4,6-trimethylphenyl)-thiopheno[3,2-*d*]pyrimidine, and 2-methyl-6-(*N,N*-dipropylamino)-8-(2,4,6-trimethylphenyl)-thiopheno[3,2-*d*]pyrimidine; the stereochemically isomeric forms, or the pharmaceutically acceptable acid addition salts thereof.
6. A composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.
7. A process for preparing a composition as claimed in claim 6 characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5 is intimately mixed with a pharmaceutically acceptable carrier.
8. A compound according to any one of claims 1 to 5 for use as a medicine.

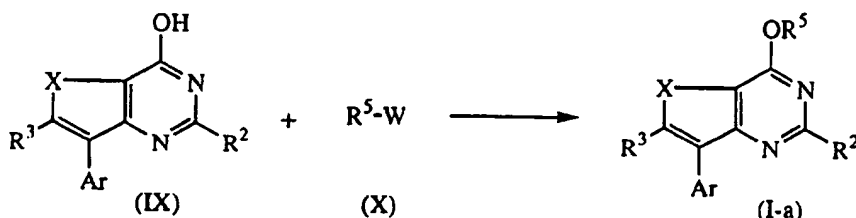
9. A compound of formula (II') wherein the radicals R^2 , R^3 and Ar are as defined in any of claims 1 to 4 and radical W' is hydroxy, halo, mesyloxy or tosyloxy; a stereoisomeric form or an acid addition salt form thereof.



10. A process of preparing a compound as claimed in claim 1, characterized by
 a) reacting an intermediate of formula (II) with an intermediate of formula (III) in a reaction-inert solvent,



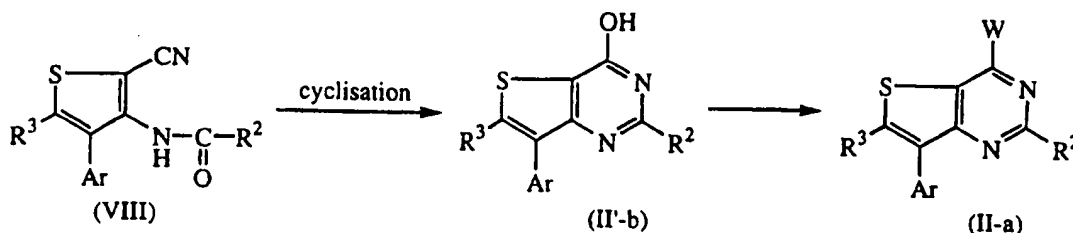
- b) *O*-alkylating an intermediate of formula (IX) with an intermediate of formula (X) in a reaction-inert solvent and in the presence of a suitable base, yielding compounds of formula (I-a), defined as compounds of formula (I) wherein R^1 is OR^5 ,



wherein in the above reaction schemes the radicals R^1 , R^2 , R^3 , R^5 and Ar are as defined in claim 1 and W is an appropriate leaving group;

or, if desired, converting compounds of formula (I) into each other following art-known transformation reactions; and further, if desired, converting the compounds of formula (I), into an acid addition salt by treatment with an acid, or conversely, converting the acid addition salt form into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

11. A process of preparing a compound of formula (II'-a) as claimed in claim 9, characterized by
 cyclizing an intermediate of formula (VIII), thereby yielding intermediates of
 formula (II'-b), defined as compounds of formula (II'-a) wherein W' is hydroxy;



and optionally converting compounds of formula (II'-b) into compounds of formula (II-a), defined as compounds of formula (II'-a) wherein W' is other than hydroxy;

wherein in the above reaction schemes the radicals R², R³ and Ar are as defined in any of claims 1 to 4, W' is hydroxy, halo, mesyloxy or tosyloxy and W is halo, mesyloxy or tosyloxy;

or, if desired, converting compounds of formula (II'-a) into each other following art-known transformation reactions; and further, if desired, converting the compounds of formula (II'-a), into an acid addition salt by treatment with an acid, or conversely, converting the acid addition salt form into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/00457

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D495/04 A61K31/505 //(C07D495/04,333:00,239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 452 002 A (DOWELANCO) 16 October 1991 cited in the application see claim 1 ---	1
X	INDIAN JOURNAL OF CHEMISTRY, vol. 33B, May 1994, pages 436-40, XP000197476 C. J. SHISHOO ET AL.: "Synthesis of some 2-substituted-6-phenyl- and 7-phenyl- thieno[3,2-d]pyrimidin-4(3H)-ones" see page 438, compound 8a ---	9
A	WO 94 13676 A (PFIZER INC.) 23 June 1994 cited in the application see abstract; claims 1,11 --- -/--	1,6,8

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

16 May 1997

Date of mailing of the international search report

02-06-1997

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00457

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 13677 A (PFIZER INC.) 23 June 1994 cited in the application see abstract; claims 1,11 ---	1,6,8
A	WO 95 33750 A (PFIZER INC.) 14 December 1995 cited in the application see abstract; claims 1,13 ---	1,6,8
A,P	WO 96 35689 A (NEUROGEN CORP.) 14 November 1996 see page 3, line 18 - line 25; claims 1-3 ---	1,6,8
A	US 5 063 245 A (M. E. ABREU ET AL.) 5 November 1991 cited in the application see claims 1,5 ---	6,8
A	EP 0 071 227 A (SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH) 9 February 1983 see claim 1 ---	1,9
A	DE 21 21 950 A (DR. K. THOMAE GMBH) 23 November 1972 see claim 1 -----	1,9

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.

PCT/EP 97/00457

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 452002 A	16-10-91	AU 651337 B AU 7392191 A CA 2039411 A JP 5310748 A	21-07-94 06-08-92 01-10-91 22-11-93
-----	-----	-----	-----
WO 9413676 A	23-06-94	AU 5666494 A CA 2150016 A CN 1097758 A CZ 9501584 A EP 0674641 A FI 935585 A HU 70505 A JP 7509726 T NO 952398 A NZ 258690 A PL 309357 A ZA 9309271 A	04-07-94 23-06-94 25-01-95 17-01-96 04-10-95 18-06-94 30-10-95 26-10-95 16-06-95 29-01-97 02-10-95 12-06-95
-----	-----	-----	-----
WO 9413677 A	23-06-94	AU 5728194 A CA 2150709 A CN 1094048 A,B CZ 9501586 A EP 0674642 A FI 935675 A HU 70426 A JP 7509728 T NO 952399 A NZ 259114 A PL 309359 A ZA 9309405 A	04-07-94 23-06-94 26-10-94 15-11-95 04-10-95 18-06-94 30-10-95 26-10-95 16-08-95 24-03-97 02-10-95 15-06-95
-----	-----	-----	-----
WO 9533750 A	14-12-95	AU 2453095 A BR 9502708 A EP 0764166 A FI 964894 A NO 965237 A	04-01-96 30-04-96 26-03-97 05-12-96 06-02-97
-----	-----	-----	-----
WO 9635689 A	14-11-96	AU 5679096 A EP 0770080 A	29-11-96 02-05-97
-----	-----	-----	-----

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/EP 97/00457

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5063245 A	05-11-91	NONE	
EP 71227 A	09-02-83	CA 1224460 A	21-07-87
		DE 3277623 A	17-12-87
		JP 4006715 B	06-02-92
		JP 58026888 A	17-02-83
		US 4584369 A	22-04-86
DE 2121950 A	23-11-72	AT 318619 B	11-11-74
		AU 4181572 A	08-11-73
		BE 783044 A	06-11-72
		BG 20593 A	05-12-75
		BG 19166 A	30-04-75
		FR 2135294 A	15-12-72
		GB 1393161 A	07-05-75
		NL 7206041 A	07-11-72
		US 3888851 A	10-06-75
		ZA 7203016 A	30-01-74